2011 Military Health System Conference

CONTACTIN 4 AS A POSSIBLE AUTISM SUSCEPTIBILITY LOCUS

The Quadruple Aim: Working Together, Achieving Success

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BACKGROUND

- Autism is the most common neurodevelopmental disorder in the US
  - Deficits in communication and social interaction skills with onset <3 yrs
  - Restricted interests and stereotypic and/or repetitive behaviors
- Up to 90% of the risk is genetic, although underlying causes remain unknown in >80% of cases; extremely heterogeneous

OBJECTIVE

To determine whether Contactin 4 (CNTN4) is an autism susceptibility gene using a carefully phenotyped local registry of autism families (CORA*) with DNA samples collected at Nationwide Children's Hospital and WPAFB

*** Central Ohio Registry for Autism**

BACKGROUND: CORA

- Recruit 250-300 carefully phenotyped probands with ASD + family members
- For each proband; complete medical history, PE, pedigree, and appropriate psychological and genetic testing
- DNA and permanent cell lines prepared and stored on all family members
- Store relevant data in password protected database (SQL) constructed for this project

BACKGROUND: CNTN4

- Synapse protein; other CNTNs and CNTNAPs implicated in autism by deletions, rare mutations, and other genetic studies
- Maps to 3p26; deletions in this region associated with MR+/-autism, rare normals
- Index family with 4 yo male with severe autism (non-verbal IQ 109; ADOS 19); female sib with mixed language disorder; ~500 kb deletion in male, sister, and nl mother at 5' end of CNTN4 on 3p26 (non-coding)

METHODS: Sequencing of CNTN4

- Sequenced 22 coding exons of CNTN4 in 87 CORA ASD affecteds (75 families)
  - 70 Males (80%); 74 Caucasian (84%)
  - Dx: autism 53 (61%), ASD 34 (39%)
  - ADOS in 76%; ADI-R in 51%
  - 68% of probands had genetics eval
- Sequenced same from 107 controls (52M/55F)

RESULTS

- 4 distinct missense variants identified in ASD cohort
  - All inherited from an unaffected parent (2Mat, 2Pat)
  - Variant found in 1 out of 2 sibs with a neurodevelopmental phenotype; not found in 1 normal sib
- 1 missense variant identified in a control
- All variants conserved thru evolution and predicted to adversely affect protein structure

CONCLUSIONS & LIMITATIONS

- Identified coding variants in 4/75 unrelated ASD patients (5.3%) and 1/107 controls (0.9%) p=0.16
- Hypothesize CNTN4 may function as an ASD susceptibility locus in combination with other genetic and/or environmental factors
- Need to study large numbers of additional affecteds and controls

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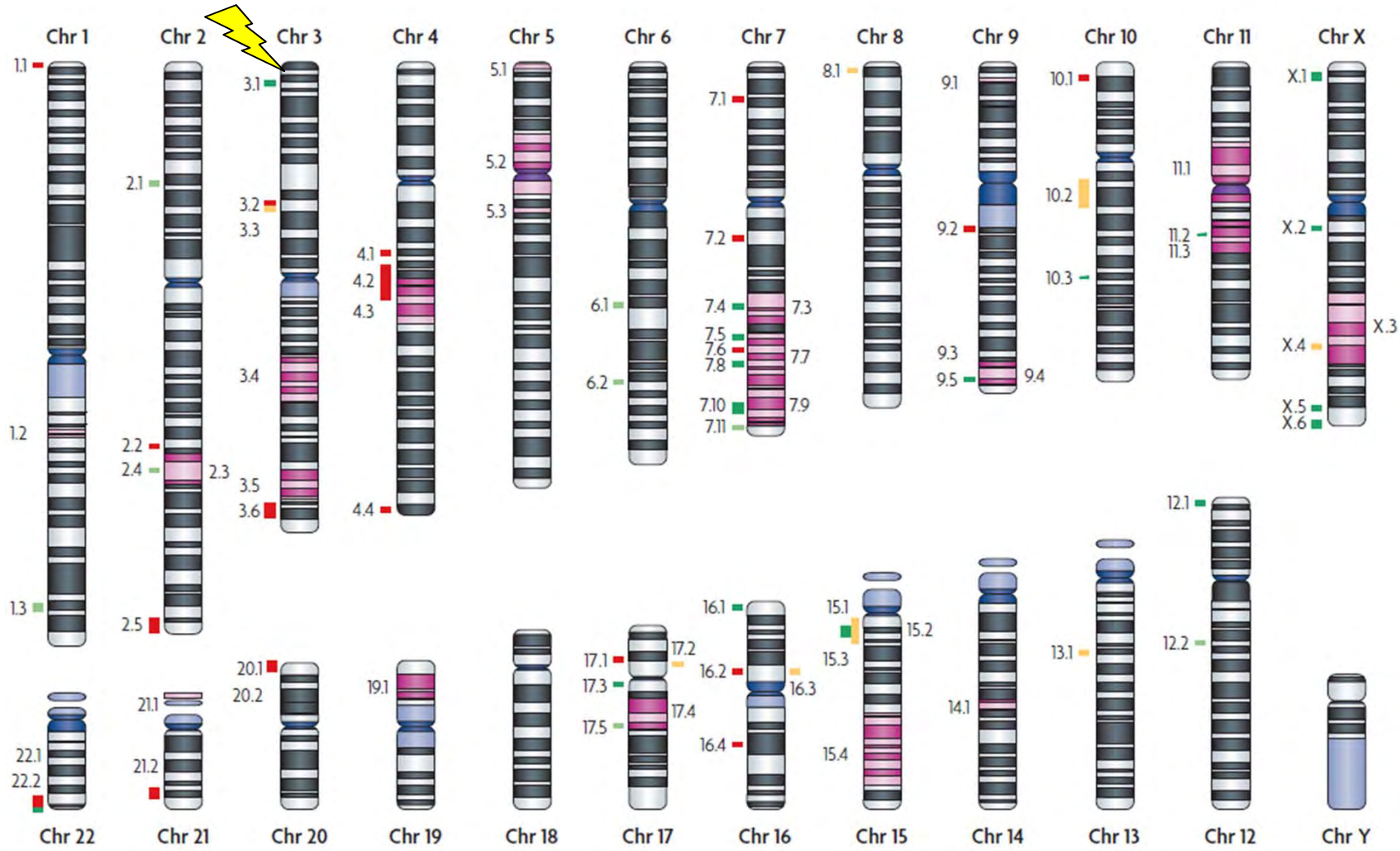
27 January 2011

Autism Spectrum Disorder - ASD

- Declared a national public health crisis
  - Nationwide 1 in 110 children have an ASD
  - In the military 1 in 88 children have an ASD
- Autistic children in military families are especially impacted
- Early identification and intervention can dramatically improve functioning, social skills, and quality of life
- Strong genetic component

Over 75 Loci Implicated in ASD



Abrahams and Geschwind 2008

The Future of Autism Research

- Define endophenotypes
  - Analysis of more homogenous subgroups
- Large scale collaborative studies
  - Common risk variants
  - Copy number variation
  - Epigenetics